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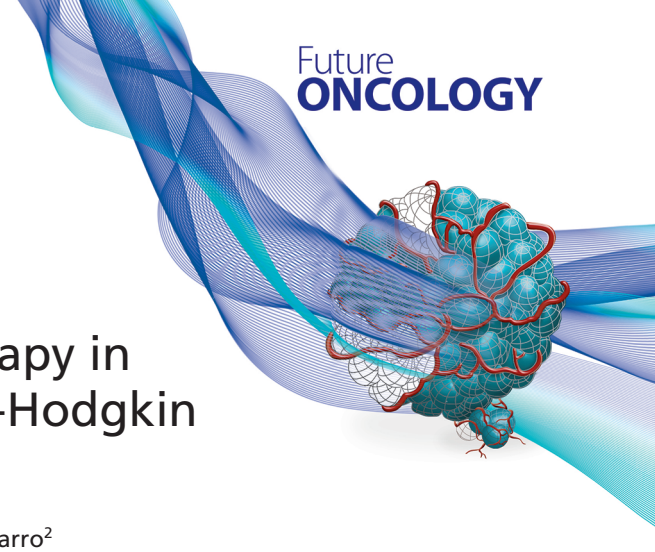

The rationale for combination therapy in patients with aggressive B-cell non-Hodgkin lymphoma: ten questions

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Rituximab plus cyclophosphamide, doxorubicin, vincristine, prednisone immunochemotherapy remains standard of care for first-line treatment of diffuse large B-cell lymphoma (DLBCL). High-dose chemotherapy and stem cell transplantation is offered to most relapsing/refractory patients who respond to salvage therapy. This Q&A review evaluates recommended management strategies for second and subsequent lines of therapy in patients with DLBCL, outlining the relative efficacies of currently available options including novel agents such as ibrutinib and CAR-T cells. The combination of pixantrone and rituximab is currently under investigation as a second-line treatment for patients ineligible for stem cell transplantation, while pixantrone monotherapy is the only therapeutic option approved for multiply relapsed and refractory DLBCL beyond the second line at this time.

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B-cell non-Hodgkin lymphoma (NHL) is a lymphoproliferative disorder originating in B lymphocytes [1]. Among B-cell NHL, the most common subtypes are diffuse large B-cell lymphoma (DLBCL), chronic lymphocytic leukemia/small lymphocytic lymphoma, follicular lymphoma, marginal zone lymphomas and mantle cell lymphoma [2]. DLBCL constitutes 25–35% of NHL [2–4], with its incidence varying according to age and geographical location [2,3,5]. For example, the incidence of DLBCL varies across the world, ranging from 3.8 per 100,000 inhabitants in Europe [5] to 6.9 per 100,000 in the USA [6]. DLBCL is a heterogeneous disease; there are at least two distinct molecular subtypes, with characteristic gene expression profiles (GEPs) and prognosis [7]. DLBCL clinical outcome can be assessed using the International Prognostic Index (IPI), a score that is determined at diagnosis using five factors (age, performance status, lactate dehydrogenase levels, stage of the disease and the presence or absence of extranodal lesions) [1,8]. Cytogenetic changes leading to coexpression of c-MYC with BCL2 and/or BCL6 (double or triple hit lymphomas) are another adverse prognostic factor [9,10].

First-line treatment

Current European Society of Medical Oncology (ESMO) standards for first-line treatment do not differ depending on the immunohistochemical, histopathological or molecular subtype of DLBCL; the recommended treatment strategy is still based on the age-adjusted IPI score (aaIPI). The role of high-dose chemotherapy (HDC) largely remains undefined and it may be considered for selected high-risk cases [3]. Choice of regimen and the additional use of radiotherapy depend on patient performance status, co-morbidities, disease stage, presence of 'bulky disease' and response to initial therapy [1,3].

First-line treatment of DLBCL typically involves the use of rituximab plus cyclophosphamide, doxorubicin, vincristine, prednisone (R-CHOP) as induction immunochemotherapy for both young and elderly fit patients [1,3]. The introduction of rituximab was a true revolution in DLBCL therapy. In randomized clinical trials, the CHOP protocol, introduced by the National Cancer Institute's 'gang of five' (George Canellos, Bruce Chabner, Phillip Schein, Vincent DeVita and Robert Young) in 1975 (Figure 1) [11], proved to be superior to all subsequent second

Figure 1. The 'gang of five' in 1973. Left to right: George Canellos, Bruce Chabner, Phillip Schein, Vincent DeVita, Robert Young.
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and third generation, more intense chemotherapy regimens. Rituximab, a chimeric mouse–human anti-CD20 antigen-binding antibody, was first approved by the US FDA in 1997 [12]. The efficacy of rituximab in combination with the CHOP regimen in DLBCL was analyzed in several studies [13,14]. In a French study by the Groupe d'Etude des Lymphomes de l'Adulte, the addition of rituximab to CHOP increased the percentage of complete remissions (CR) from 63 to 76%, 2-year event-free survival (EFS) from 38 to 57% and overall survival (OS) from 57 to 70% in elderly patients [13]. Efficacy has also been demonstrated in younger patients with DLBCL. In the MInT study (Mabthera® International Trial) in low-risk patients aged less than 60 years, with stages II–IV and stage I bulky disease, the addition of rituximab to CHOP increased the 3-year EFS from 59 to 79% [14]. Most of the patients participating in randomized trials had low or intermediate risk according to IPI, but there are retrospective observations also confirming the efficacy of rituximab in high-risk cases [15]. High-risk patients, according to aaIPI, may be considered for more intensive treatment with HDC followed by autologous stem cell transplantation (ASCT) as first-line consolidation [1,3,16]. Although some authors preferred R-DA-EPOCH (rituximab and dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) in high-risk patients, no superiority of this protocol was demonstrated in a randomized comparison to R-CHOP in the CALGB/Alliance 50303 trial [17].

For unfit or frail patients, doxorubicin can be substituted with other drugs (liposomal doxorubicin, gemcitabine or bendamustine) [3]. Elderly patients who cannot be treated with doxorubicin are possibly more numerous than anticipated; for example, in a study of 9438 patients with DLBCL, only 3164 (42%) received doxorubicin-based chemotherapy [18]. Substitution of doxorubicin with pixantrone may be useful in this setting, with a Phase II study indicating similar progression-free survival (PFS; not reached vs 40 months; hazard ratio [HR]: 1.02; 95% CI: 0.60–1.76; p = 0.934) and EFS, with a lower incidence of severe cardiac events with first-line R-CPOP (rituximab, cyclophosphamide, pixantrone, vincristine) versus R-CHOP [19]. Alternatives include R-miniCHOP or BR regimens [20,21].

An attempt to improve efficacy by replacing rituximab with obinutuzumab in combination with CHOP as first-line therapy in patients with DLBCL failed to demonstrate improved PFS in the Phase III GOYA trial [22]. After a median follow-up duration of 29 months, PFS events (28.5 vs 30.2%; HR: 0.92; 95% CI: 0.76–1.11; p = 0.39) and 3-year PFS rates (70 vs 67%) were similar in obinutuzumab- and rituximab-treated patients [22].

Follow-up of patients after first-line therapy

Guidelines recommend that patients with CR after induction chemotherapy receive regular follow-up (physical examination, blood counts) every 3–6 months for 5 years, with computed tomography (CT) no more than once every 6 months for up to 2 years after completion of treatment [1,3]. Since later relapses are less frequent [23], a thorough clinical assessment does not need to include imaging studies in asymptomatic patients [24,25].

Relapsed/refractory disease

Patients who do not achieve a CR with induction chemotherapy are treated as those with relapsed/refractory disease [1,3]. Patients with relapsed/refractory disease receive second-line salvage chemotherapy followed, in responding patients, by consolidation HDC/ASCT [1,3]. Those who are not suitable for HDC/ASCT may receive subsequent lines of chemotherapy [1,3].

Q&A

How does the cell of origin impact current management strategies?

Distinct molecular subtypes of DLBCL, arising from distinct genetic pathways [26], have been identified using GEPs [27–29]. These include germinal center B-cell like (GCB), activated B-cell like (ABC) and type 3 (remaining unclassified cases that are neither GCB nor ABC subtypes) [27–29].

Subsequently, with the discovery of more favorable outcomes in GCB than in ABC subtypes [28,30–32], cell of origin has become an important prognostic factor in guiding treatment decisions. Better prognosis was observed with GCB than with ABC in patients treated with anthracycline-based chemotherapy [28]. Similarly, the GCB subtype was associated with significantly better OS than the non-GCB subtype in patients receiving HDC/ASCT ($p = 0.04$) [30]. Also, significantly improved PFS and OS were observed with GCB versus ABC subtypes in patients receiving R-CHOP (both $p < 0.001$) [32], and the Collaborative Trial in Relapsed Aggressive Lymphoma (bioCORAL) subanalysis suggested a possible advantage of R-DHAP (rituximab, dexamethasone, cytarabine, cisplatin) in the GCB subtype [31]. Patients with GCB DLBCL treated with R-DHAP had improved 3-year rates for PFS (52 vs 32%; $p = 0.01$) and OS (61 vs 45%; $p = 0.0813$) compared with those with non-GCB DLBCL [31]. Whereas no significant differences in 3-year PFS (31 vs 27%) or OS (50 vs 49%) were observed between GCB and non-GCB DLBCL subtypes treated with R-ICE (rituximab, ifosfamide, carboplatin, etoposide) [31]. However, cell-of-origin identification failed to predict survival in patients with chemosensitive or chemoresistant DLBCL treated with HDC/ASCT [33]. Chronic active B-cell receptor signaling has been shown to activate NF-κB in ABC DLBCL [34], and objective responses are greater with ibrutinib, a small-molecule inhibitor of Bruton's tyrosine kinase (BTK), in ABC DLBCL than in GCB DLBCL [34].

Presently, the upfront standard of care remains the same for both GCB and non-GCB subtypes, and cell-of-origin analyses (GEP, immunohistochemistry) are not yet recommended for routine clinical use [1,3]. Newer methods, which examine a limited set of genes to distinguish ABC and GCB subtypes, have been validated versus standard gene expression, and are now used in the setting of clinical trials [35,36].

DLBCLs are also associated with concurrent MYC aberrations and BCL2 and/or BCL6 translocations [37–41]. Particularly, poor prognosis is observed in about 5% of patients with DLBCL who have a double rearrangement in the MYC and BCL2 genes (double hit), and in particular with an additional translocation of the BCL6 gene (triple hit) [38–41]. Thus, MYC and BCL2 protein expression has emerged as a marker of poor prognosis in patients with *de novo* DLBCL treated with CHOP ± rituximab [42–46], with more frequent dual expression of MYC/BCL2 observed in the ABC subtype [44]. In the relapsed/refractory setting, outcomes after treatment with R-ICE or R-DHAP followed by HDC/ASCT were worse in MYC+ than in MYC- patients [37].

What do the guidelines say, & what are the clinical options for second-line treatment of NHL?

Guidelines divide patients into transplant eligible versus ineligible [1,3]. All alternatives to ASCT are considered palliative or patients are encouraged to participate in clinical trials of novel drugs (Table 1). In patients eligible for HDC/ASCT, preferred second- and subsequent-line regimens include: DHAP (dexamethasone, cytarabine,

Table 1. Recommended treatment strategies for relapsed diffuse large B-cell lymphoma.

Patients eligible for transplant	Patients ineligible for transplant
First relapse/progression	
• Platinum-based chemotherapy regimens (i.e., R-DHAP, R-ICE, R-GDP) as salvage treatment • For chemosensitive patients: R-HDC with ASCT as remission consolidation • Consider allogeneic transplantation in patients relapsed after R-HDC with ASCT or in patients with poor-risk factors at relapse	• Platinum- and/or gemcitabine-based regimens • Clinical trials with novel drugs
≥2 relapses/progression	
• Allogeneic transplantation • Clinical trials with novel drugs	• Clinical trials with novel drugs • Palliative care • Pixantrone

ASCT: Autologous stem cell transplant; R-DHAP: Rituximab, dexamethasone, cytarabine, cisplatin; R-GDP: Rituximab, gemcitabine, dexamethasone, cisplatin; R-HDC: Rituximab, high-dose chemotherapy; R-ICE: Rituximab, ifosfamide, carboplatin, etoposide.
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cisplatin), ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin), GDP (gemcitabine, dexamethasone, cisplatin), GemOx (gemcitabine, oxaliplatin), ICE or MINE (mitoxantrone, ifosfamide, mesna, etoposide), all with or without rituximab [1,3]. There is no clear superiority between different salvage regimens [47,48], but if patients are to undergo stem cell transplantation (SCT), confirming response to preceding therapy is necessary [49–51].

Patients ineligible for HDC/ASCT receive, with palliative intent, single-agent rituximab or other chemotherapy regimens ± rituximab (Table 1) [1,3]. Preferred second- and subsequent-line regimens include: bendamustine ± rituximab; brentuximab vedotin for $CD30^+$ disease; CEPP (cyclophosphamide, etoposide, prednisone, procarbazine) ± rituximab; CEOP (cyclophosphamide, etoposide, vincristine, prednisone) ± rituximab; DA-EPOCH ± rituximab; GDP ± rituximab; GemOx ± rituximab; gemcitabine ± rituximab; gemcitabine, vinorelbine ± rituximab; lenalidomide ± rituximab; and rituximab [1,3,52]. The combination of pixantrone ± rituximab is currently under investigation in this setting in a Phase III trial [53].

What is the right treatment for each patient?

Clinical status and known risk factors are useful when choosing salvage therapies. In the CORAL trial, efficacy (clinical response rates; 3-year rates of EFS, PFS and OS) after salvage therapy was affected by several independent factors [48]. These factors included: secondary age-adjusted IPI (saaIPI) score (<2 vs >1), short relapse time from diagnosis (<12 vs >12 months) and prior rituximab treatment. The saaIPI comprises three risk factors: elevated lactate dehydrogenase levels, disease stages III–IV and Karnofsky performance status less than 80% [54].

Recently, immunohistochemistry has become a tool that can help choose treatment for patients more accurately [55]. Though cell of origin, MYC, BCL2 and BCL6 analyses are not yet widely used, they may play an important role in the near future.

SCT versus no SCT?

SCT is assumed to be better than standard-dose therapy for relapsed disease [51]; thus, transplant is the goal in patients responding to second-line therapy (CR or a good PR) [56]. Two studies have examined the value of SCT in patients with relapsed DLBCL [48,57]. The first of these, the PARMA trial, was conducted in the 1980s, with ASCT allowing for longer PFS in 50% of responding patients [57]. The later CORAL trial was conducted in the rituximab era, when fewer patients relapse but have truly refractory disease [48]. In this study, less than 20% of patients with refractory disease within the first 12 months after R-CHOP were able to be salvaged [48].

However, the advent of alternative regimens and novel targeted drugs is challenging the role of SCT in some patient subsets [56,58]. A recent study comparing SCT versus no SCT after an abbreviated course of rituximab-dose-dense chemotherapy followed by consolidation with R-MAD (rituximab plus high-dose cytarabine plus mitoxantrone plus dexamethasone) and high-dose BEAM (carmustine, etoposide, cytarabine, melphalan) showed that the significantly improved 2-year EFS observed with SCT (71 vs 62%; HR: 0.65; p = 0.012) did not translate into a significant improvement in 5-year OS (78 vs 77%; HR: 0.98; p = 0.91) [58]. Follow-up in studies of novel agents is relatively short and, unlike SCT, none of these drugs have demonstrated a curative potential [56]; however, there may be the potential to postpone SCT in patients with deep and durable responses in the future.

If a patient is ineligible for transplant, the final outcome changes dramatically. Among patients who are not candidates for SCT, response rates are low, CR are rare and expected survival is less than 6 months [59]. For third-line treatment following relapse or resistance, ESMO guidelines recommend allogeneic SCT as an option for transplant-eligible patients [3]. In the past decade, eligibility for allogeneic SCT has improved mainly due to the use of reduced-intensity conditioning [60–62].

What are the eligibility criteria for SCT in patients with NHL?

Eligibility for SCT varies across countries and institutions. Ultimately, decisions regarding transplant eligibility should be made on a case-by-case basis, based on a risk–benefit assessment and the needs and wishes of the patient. To best determine the likelihood that a patient is a candidate for SCT, a pretransplant assessment must establish the extent of disease and provide information about the individual's co-morbidities that are likely to have an impact on outcomes.

Among the individual factors or co-morbidities that have an impact on the decision, there are some that should always be included and based on performance status, co-morbidity, age, compliance, extent and status of disease, as well as the sensitivity of the tumor to standard therapy [63].

What is the rationale for various combinations in the second-line treatment of NHL?

In fit patients, second-line chemotherapy is considered a bridge to SCT [56], with patients achieving a CR or PR going on to receive HDC/ASCT [1,3]. It is believed that response to second-line chemotherapy likely predicts sensitivity to HDC, with achievement of CR prior to transplantation associated with better outcomes than achievement of PR [49,50]. Thus, the efficacy of second-line therapies is generally judged on the basis of clinical response rates, as well as transplant-related factors (mobilization and harvesting of sufficient stem cells) [47].

Chemotherapy regimens should contain platinum, for example, R-DHAP, R-ESHAP, R-ICE. No significant differences in EFS and OS have been observed between these regimens after three cycles [48]. Also, R-GDP has a similar efficacy to R-DHAP, but with lower toxicity and better quality of life [64]. BEAM is the most commonly used consolidation high-dose regimen [3]. Treatment preferences depend on a number of factors, such as patient age, time to relapse, IPI score and prior rituximab therapy, which have been shown to affect response rates in the salvage setting [47,50,54,65–67]. In the high-risk population of relapsed NHL, the PREBEN/PEBEN salvage schedule (pixantrone, [rituximab], etoposide, bendamustine) is feasible (outpatient regimen) and the preliminary efficacy data are promising [68].

This approach is problematic when the patient does not respond to the treatment, or is considered ineligible for HDC/ASCT due to advanced age or co-morbidities [47]. Prognosis is poor in patients with an inadequate response to salvage therapy [51], and there is no particular standard of care in these patients [69]. They generally receive palliative treatment with platinum- and/or gemcitabine-based regimens, or are treated with novel drugs in clinical trials [3]. Less intensive regimens with demonstrated efficacy in patients with NHL include bendamustine + rituximab [70,71], lenalidomide + rituximab [72,73], and GemOx + rituximab [74–77]. In addition, several monotherapies, including gemcitabine [78], rituximab [79], lenalidomide [80,81], bendamustine [82], ibrutinib [34], bortezomib [83], pixantrone [69] and oxaliplatin [84], have shown encouraging efficacy with relatively mild toxicity in patients with relapsed/refractory aggressive NHL.

What are the comparative efficacies of current chemotherapy options?

Efficacy outcomes among the current chemotherapy options mentioned above are similar. As demonstrated in the CORAL study, outcomes with the widely used salvage regimens R-DHAP and R-ICE are similar [48]. However, while R-GDP has similar efficacy to R-DHAP, toxicity appears to be lower with R-GDP [64]. R-DHAP also seems to have a survival advantage in the GCB subtype of DLBCL [31].

Based on post-transplantation results of the CORAL trial, maintenance with rituximab after ASCT is not recommended [85]. Rituximab maintenance every 2 months for 1 year was compared with observation alone in patients with refractory or relapsed $CD20^+$ DLBCL previously treated with HDC/ASCT following a response to R-ICE or R-DHAP [85]. No differences in EFS were observed between treatment arms, but a 15% increase in serious adverse events and an excess of deaths due to possible immunodeficiency-related infection was reported in the rituximab arm [85].

Response rates in studies of pixantrone-containing therapies (e.g., pixantrone monotherapy, PSHAP [pixantrone, methylprednisolone, cisplatin and cytosine arabinoside]) [86,87] are favorable compared with other salvage thera-

Table 2. Response rates with salvage therapies in patients with relapsed/refractory diffuse large B-cell lymphoma.

Study (year)	Regimen	Number of prior regimens	ORR (%)	CR (%)	Ref.
Borchmann *et al.* (2011)	CPOP	1; 2; >2	73	47†	[89]
Kewalramani *et al.* (2004)	R-ICE	1	78	53	[49]
Gisselbrecht *et al.* (2010)	R-ICE vs R-DHAP	1	64 vs 63	36 vs 40†	[48]
Jermann *et al.* (2004)	R-EPOCH	1–4	68	28	[88]
Crump *et al.* (2014)	R-DHAP vs R-GDP	≥3	44.1 vs 45.1	14.3 vs 13.5	[64]

†Includes unconfirmed CR.
CR: Complete response; ORR: Overall response rate; R-CPOP: Rituximab, cyclophosphamide, pixantrone, vincristine, prednisone; R-DHAP: Rituximab, dexamethasone, cytarabine, cisplatin; R-EPOCH: Rituximab, etoposide, vincristine, doxorubicin, prednisone, cyclophosphamide; R-GDP: Rituximab, gemcitabine, dexamethasone, cisplatin; R-ICE: Rituximab, ifosfamide, carboplatin, etoposide.

Table 3. Efficacies of single-agent therapies in patients with relapsed/refractory non-Hodgkin lymphoma.

Treatment	Lymphoma type	Patients (n)	Previous therapies	ORR (%)	CR/CRu (%)	Median PFS (months)	Ref.
Gemcitabine	RR aNHL	31	1–3	20	0	6.0†	[78]
Rituximab	RR aNHL	21	Median 2.5	38	5	3.8‡	[79]
Lenalidomide	RR aNHL	217	Median 3	35	13	3.7	[80]
	RR DLBCL	108	Unknown	28	7	2.7	
Lenalidomide	RR aNHL	49	Median 4	35	12	4.0	[81]
Bendamustine	RR aNHL	18	1–4	44	17	NR	[82]
Ibrutinib	DLBCL	80	3	25	10	1.6	[34]
	ABC DLBCL	38	3	37	16	2.0	
Bortezomib	RR NHL (excluding MCL)	27	Median 4	19	10	1.8§	[83]
Oxaliplatin	RR NHL¶	30	Median 2	27	7	3.0#	[91]
	RR aNHL	22	Unknown	32	9	2.1#	
Pixantrone vs active comparator	RR aNHL	70	Median 3	37	20	5.3	[69]
		70	Median 3	14	5.7	2.6	

†Time to progression in responders.
‡Event-free survival.
§Time to progression.
¶Includes eight patients with indolent NHL.
#Failure-free survival.
ABC: Activated B-cell like; aNHL: Aggressive non-Hodgkin lymphoma; CR: Complete response; CRu: Unconfirmed complete response; DLBCL: Diffuse large B-cell lymphoma; iNHL: Indolent non-Hodgkin lymphoma; MCL: Mantle cell lymphoma; NR: Not reported; ORR: Overall response rate; PFS: Progression-free survival; RR: Relapsed/refractory.

pies [48,88]. In particular, in the trial evaluating the PSHAP regimen, six out of 11 responding patients were able to proceed to ASCT [86]. Response rates of relapsed or refractory lymphoma to salvage regimens are shown in Table 2 [48,49,64,88,89].

What are future options?

Future options – if ongoing clinical evaluations have positive outcomes – may include the combination of pixantrone and rituximab, BTK inhibitors, immunomodulatory drugs, novel monoclonal antibodies and CAR-T cells immunotherapy [34,53,90]. The second-line treatment landscape is evolving rapidly. The Phase III PIX306 study, conducted as a postauthorization requirement to confirm the efficacy of pixantrone in transplant-ineligible patients with relapsed aggressive DLBCL, is comparing the efficacy and tolerability of second-line pixantrone plus rituximab with gemcitabine plus rituximab [53]; results are expected in summer 2018. Combination pixantrone plus rituximab could be an interesting option for a subgroup of patients with previous co-morbidities who may be unable to receive an intense chemotherapy. In terms of single-agent therapy in relapsed/refractory NHL, pixantrone has been shown to be very active, with a comparable or better CR/unconfirmed CR rate than other agents [34,78–83,91], with a manageable toxicity profile and the potential for use in patients who are close to reaching their threshold for maximal anthracycline cumulative dose (Table 3) [53,69,92]. In conclusion, pixantrone is a good option for patients with DLBCL relapsing after ASCT.

Novel targeted agents like ibrutinib and CAR-T cells have demonstrated prolonged remissions with very good safety profiles [34,90]. The Phase I/II ZUMA-1 study, evaluating the safety and efficacy of anti-CD19 CAR-T cells in nine patients with refractory aggressive NHL, demonstrated an objective response rate (ORR) of 71% within 1 month of cell infusion, including CR in 57% of patients [90]. Three patients experienced ongoing CR at 12 months' post-treatment [90]. Long-term results of the ZUMA-1 study showed a best ORR of 82%, and a best CR rate of 58%, with 40% of patients remaining in CR; in the cohort of patients continuing in the study at 15.4 months, ORR was 42% [93,94]. Ibrutinib demonstrated encouraging response rates among 80 patients with relapsed or refractory *de novo* DLBCL, especially among those with the ABC subtype [34]. In the overall and ABC patient populations, 25 and 37% of patients achieved an objective response, respectively. Corresponding rates of CR were 10 and 16%, and PRs were 15 and 10% [34]. A randomized Phase III study of R-CHOP with or without ibrutinib in newly diagnosed patients with non-GCB DLBCL is ongoing (NCT01855750) [34].

Several studies have examined the use of monoclonal antibodies in combination with lenalidomide for the treatment of patients with relapsed/refractory DLBCL [95–97]. Compared with single-agent lenalidomide, which has a CR of 10% (ORR: 28%) and a median PFS of 13.6 weeks [98], lenalidomide in combination with rituximab was associated with a CR of 22% (ORR: 28%) and a median PFS of 2.8 months [95], lenalidomide plus obinutuzumab had a CR of 16% (ORR: 45%) [96] and lenalidomide plus MOR208 had a CR of 32% (ORR: 56%) [97].

Is participation in clinical trials a relevant second-line option?

Guidelines propose clinical trials as a relevant option for patients who are not eligible for ASCT [1,3], but it is also known that no more than 30% of oncologic patients will have the chance to participate in a clinical trial during their lifetime [99]. There are many known barriers to clinical trial participation. Many oncologists do not offer the opportunity to participate in clinical trials to their patients [100–103]; this could be due to a lack of physician knowledge about available clinical trials [101]. It has been estimated that only approximately 20% of cancer patients are eligible for participation in cancer clinical trials [101], which is, in part, due to the growing number of biomarker-selected or -stratified trials, resulting in more patients failing screening, either due to an ineligible molecular profile or a lack of tissue for analysis [99]. Limited personnel resources [104], logistical issues such as cost and lack of transportation in rural or underserved populations [101,102], patient concerns regarding the methods of the trial [102,103], and patient concerns regarding interruptions to their lifestyle [102,103] are also known barriers to clinical trial participation.

Despite these barriers, it is important to participate in clinical trials. Between 2005 and 2011, one in ten cancer trials on ClinicalTrials.gov closed prematurely due to poor accrual and slow recruitment [99]. While it is a patient's decision to participate in clinical trials or not, the National Cancer Institute and American Society of Clinical Oncology considers rapid completion of clinical trials a societal imperative [100].

What is the role of PET-CT scan in the follow-up of patients outside the setting of RCTs?

PET-CT is used widely in clinical trials and in diagnosing the disease, but there are still controversies regarding the widespread use of this tool in follow-up [105,106]. While PET-CT is more accurate than contrast-enhanced CT, with increased sensitivity for nodal and extranodal sites, in practice, contrast-enhanced CT is often carried out before PET-CT [3]. Also, the application of PET-CT to response assessment is limited to histologies where there is reliable uptake of fluorodeoxyglucose in active tumors [1,106]. Furthermore, revised response criteria have only been validated for DLBCL and Hodgkin lymphoma [1]. PET-CT has been shown to predict response in DLBCL, but more intensive chemotherapy has failed to improve outcomes for patients with interim PET-CT-positive scans [107]. To date, routine surveillance PET-CT is not recommended. High-risk patients with curative options may potentially mandate more frequent evaluation. Results of PET before high-dose treatment are correlated to clinical outcome [3].

Conclusion & future perspective

This Q&A review evaluates recommended management strategies for second and subsequent lines of therapy in patients with DLBCL, outlining the relative efficacies of currently available options including novel agents such as alternative cytostatics (pixantrone), BTK inhibitors, immunomodulatory drugs, novel monoclonal antibodies and CAR-T cells. As discussed above, future options for the treatment of DLBCL may be changed, both in the first-line and relapsing/refractory setting. The second-line treatment landscape is evolving rapidly, with the combination of pixantrone and rituximab currently under investigation as a second-line treatment for patients ineligible for SCT.

Executive summary

- B-cell non-Hodgkin lymphoma (NHL) is a lymphoproliferative disorder originating in B lymphocytes; one of the most common subtypes of NHL is diffuse large B-cell lymphoma (DLBCL).

First-line treatment

- European Society of Medical Oncology guidelines for first-line treatment of DLBCL recommend treatment based on age-adjusted International Prognostic Index scores.
- First-line treatment of DLBCL typically involves the use of rituximab plus cyclophosphamide, doxorubicin, vincristine, prednisone (R-CHOP) as induction immunochemotherapy.
- For unfit or frail patients, alternative protocols may be considered, such as R-miniCHOP, R-COMP (with doxorubicin substituted with its liposomal formulation) and R-gemcitabine or R-bendamustine.

Follow-up of patients after first-line therapy

- Guidelines recommend that patients with a complete response after first-line therapy are followed every 3–6 months for 5 years.

Relapsed/refractory disease

- Refractory patients are those who do not achieve a complete response with induction chemotherapy. Fit relapsing/refractory patients should receive second-line salvage chemotherapy followed – in chemosensitive cases – by consolidation high-dose chemotherapy/autologous stem cell transplantation (ASCT). Alternative chemotherapy regimens should be considered in frail individuals and those who do not respond to salvage chemotherapy.

Q&A

How does the cell of origin impact current management strategies?

- There are at least three distinct subtypes of DLBCL, with different genetic pathways, including germinal center B-cell like (GCB), activated B-cell like and type 3. As the GCB subtype is associated with more favorable outcomes, cell-of-origin analysis has become an important prognostic factor. However, the upfront standard of care remains the same for GCB- and non-GCB subtypes. Cell-of-origin analyses are not yet recommended for routine clinical use.
- DLBCL prognosis is also associated with concurrent MYC aberrations and BLC2 and/or BCL6 translocations, which can affect treatment outcomes.

What do the guidelines say, & what are the clinical options for second-line treatment of NHL?

- Guidelines divide patients by transplant eligibility. For noneligible patients, all available treatments are considered palliative. For eligible patients, multiple second- and subsequent-line regimens are available, with no clear superiority between different salvage therapies.

What is the right treatment for each patient?

- When choosing salvage therapy, clinical status and known risk factors should be considered.
- In patients refractory to chemotherapy, when stem cell transplantation (SCT) is not recommended alternative regimens with novel agents should be explored.

SCT versus no SCT?

- While SCT is usually better than standard-dose therapy for relapsed/refractory disease, responding to preceding salvage regimen, its role as consolidation therapy in high-risk cases remains controversial. Alternative regimens or novel targeted drugs may have the potential to postpone SCT in patients with deep and durable responses.

What are the eligibility criteria for SCT in patients with NHL?

- Eligibility varies across countries and institutions, and eligibility should ideally be made on a case-by-case basis using risk–benefit assessments and taking the patient's wishes into account.
- Performance status, comorbidity, age, compliance, extent of disease and – most importantly – tumor sensitivity should all be considered when determining SCT eligibility.

What is the rationale for various combinations in the second-line treatment of NHL?

- Second-line therapy is considered a bridge to ASCT, with the response observed with second-line treatment associated with sensitivity to high-dose chemotherapy.
- Chemotherapy regimen should contain a platinum; however, no significant differences in event-free survival and overall survival have been shown between various platinum-containing regimens.

What are the comparative efficacies of current chemotherapy options?

- The efficacy outcomes of the current chemotherapy options are similar, while response rates in studies of pixantrone-containing therapies (i.e., PREBEN or PSHAP) are favorable compared with other salvage therapies, although further clinical trials are necessary to confirm these preliminary results.

What are future options?

- If ongoing clinical evaluations have positive outcomes, future options for the treatment of DLBCL may include the combination of pixantrone and rituximab, Bruton's tyrosine kinase inhibitors, immunomodulatory drugs, novel monoclonal antibodies and CAR-T cells immunotherapy.

Is participation in clinical trials a relevant second-line option?

- Guidelines propose participation in clinical trials for patients who are not eligible for ASCT; however, no more than 30% of oncologic patients get the opportunity to do so as there are many barriers to clinical trial participation.

What is the role of PET-CT scan in the follow-up of patients outside the setting of RCTs?

- PET-CT is widely used in RCTs and for disease diagnosis; however, there is still widespread controversy on using this tool in follow-up.
- To date, routine surveillance using PET-CT is not recommended; however, high-risk patients with curative options may potentially mandate more frequent evaluation.

Supplementary data

A video abstract and transcript are available as an accompaniment to this paper. To view the supplementary transcript for this please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/fon-2018-0388

Author's contributions

W Jurczak contributed to the design, critically revised the manuscript, and read and approved drafts. M Długosz-Danecka read and approved drafts and critically revised manuscript. F Rivas Navarro helped in the design, read and approved drafts and critically revised manuscript.

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